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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/540,466	03/31/00	RIPAMONTI U	STK-6

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EXAMINER	
NICKOL,G	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/540,466	Applicant(s) RIPAMONTI ET AL.	
	Examiner Gary B. Nickol Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 5-14-01 .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) 1,18 and 20 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 2-17 and 19 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

The Election filed May 14, 2001 (Paper No. 7) in response to the Office Action of April 10, 2001 is acknowledged and has been entered. Claims 1-20 are pending in the application and Claims 1, 18, 20 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 2-17, 19 are currently under prosecution. (It is noted that applicant has elected the following species: OP-1, bFGF, and simultaneous administration. Accordingly, Claims 18, and 20 have been withdrawn as drawn to non-elected species.)

Applicant's election with traverse of Group II, claims 2-20 in Paper No 7 is acknowledged. The traversal is on the ground(s) that the inventions have not been shown to be independent and the examination of all groups would not impose a serious burden on the examiner. This is not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in Paper No. 6.

As to the question of burden of search, the inventions are classified differently, necessitating different searches in the US Patent shoes. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Specification

The Brief Description of the Drawings (pages 8-12) is objected to for referring to colored staining in the drawings (i.e. blue staining collagen, page 10, line 5) as the drawings were submitted in black and white and cannot be analyzed for color.

The specification is further objected to on page 42, lines 15-20 for improper disclosure of amino acid sequences without a respective sequence identifier, i.e. a SEQ ID NOs:. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. In the absence of a sequence identifier for each sequence, Applicant must provide a computer readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d).

ok

Claim Objections

Claim 13 is objected to because of the following informalities: Claim 13 recites "selected from the group consisting acidic". Appropriate correction is required by amending the claim to recite "selected from the group consisting of".

o/k

Claims 5-7, 9, and 11-12 are objected to as being dependent from non-elected Claim 1. Appropriate correction is required. –

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 8, 10, 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for combining specific morphogenic proteins with morphogenic protein stimulatory factors to improve angiogenesis, does not reasonably provide enablement for combining amino acid sequence variants of morphogenic proteins and or amino acid sequence variants of morphogenic protein stimulatory factors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method for improving the angiogenic inductive activity of a morphogenic protein in a mammal by co-administering with the morphogenic protein an effective amount of a morphogenic protein stimulatory factor including amino acid sequence variants of both morphogenic proteins and morphogenic protein stimulatory factors.

This includes the combination of a whole universe of polypeptides whose amino acid sequences may contain a multitude of variations including deletions, substitutions, and additions as well as a whole universe of polypeptides with any degree of homology to known morphogenic proteins and or morphogenic protein stimulatory factors.

The specification teaches that other useful morphogenic proteins include polypeptides having at least 70% sequence homology with a known morphogenic protein. These include biologically active variants of any known morphogenic protein, including variants containing conservative amino acid changes. (page 17). The specification further teaches that preferred morphogenic protein stimulatory factors include hormones, cytokines and growth factors and those compounds listed on page 47, including amino acid variants thereof (page 57, line 21).

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to any polypeptide with or without sequence homology to known morphogenic proteins and or morphogenic protein stimulatory factors with or without the biological properties representative of what is claimed, and applicant has not enabled all of these types of modified proteins because it has not been shown that these modified proteins are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid

sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use any and all polypeptide variants with or without sequence similarity to the morphogenic proteins. Therefore, in view of the speculative nature of the invention, the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2, 4-6, 9-14, 16-17, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Duneas et al. (Growth Factors, Vol. 15, 1998, pages 259-277, IDS).

The claims are drawn to a method for improving the angiogenic inductive activity of a morphogenic protein in a mammal by co-administering with the morphogenic protein an effective amount of a morphogenic protein stimulatory factor (Claim 2); wherein the morphogenic protein stimulatory factor has synergistic effects on angiogenesis by the morphogenic protein (Claim 4); wherein the morphogenic protein is an osteogenic protein that is capable of inducing angiogenesis (Claim 5); wherein the morphogenic protein comprises an amino acid sequence selected from the group consisting of OP-1 (Claim 6); wherein the morphogenic protein is a dimeric species (Claim 9); wherein the dimeric species is OP-1 (Claims 10, 11); wherein the morphogenic protein is produced by the expression of a recombinant DNA molecule in a host cell (Claim 12); wherein the morphogenic protein stimulatory factor comprises at least one compound selected from the group consisting of TGF-β (Claims 13-14, 16); wherein the morphogenic protein and the morphogenic protein stimulatory factor are administered simultaneously to a target locus (Claim 17); wherein the target locus is a vascular tissue defect (Claim 19).

Duneas et al. teach the simultaneous administration of a morphogenic protein- OP1 (homodimeric OP-1; column 1, page 261) and a morphogenic protein stimulatory factor (TGF-β) to a target locus wherein the target locus is a vascular tissue defect (abstract). Duneas et al. further teach that the two proteins interact synergistically (page 268) and that the data "suggests that the two morphogens interact synergistically to induce angiogenesis and vascular invasion" (column 1, page 274). Duneas et al. further teach that since angiogenesis is a "prerequisite" for osteogenesis, enhanced vascularization may be part of the mechanism whereby OP-1 and TGF-β synergize in hetertopoic bone induction (column 1, page 274).

Although Duneas et al. does not specifically teach that the morphogenic protein, OP-1, is produced by the expression of a recombinant DNA molecule in a host cell, the claimed peptide appears to be the same as the prior art , absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed protein was produced differently from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 2-5, 7, and 12-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Goldberg et al. (US Patent 6,013,624; October 1993, IDS) as evidenced by Amano et al. (Arch Oral Biol., Vol. 44, No. 11, November 1999, abstract only).

The claims are drawn to a method for improving the angiogenic inductive activity of a morphogenic protein in a mammal by co-administering with the morphogenic protein an effective amount of a morphogenic protein stimulatory factor (Claim 2); wherein the morphogenic protein stimulatory factor has additive effects on angiogenesis by the morphogenic protein (Claim 3); wherein the morphogenic protein stimulatory factor has synergistic effects on angiogenesis by the morphogenic protein (Claim 4); wherein the morphogenic protein is an osteogenic protein that is capable of inducing angiogeneis (Claim 5); wherein the morphogenic protein is a monomeric species (Claim 7); wherein the morphogenic protein is produced by the expression of a recombinant DNA molecule in a host cell (Claim 12); wherein the morphogenic protein stimulatory factor comprises at least one compound selected from the group consisting of bFGF (Claims 13-15).

Goldberg et al. teach a method for improving the angiogenic inductive activity of a morphogenic protein (In this case the morphogen is called scatter factor, column 1, line 44) in a mammal by co-administering with the morphogenic protein an effective amount of a morphogenic protein stimulatory factor (FGF). (see column 8, lines 7-11; column 3, lines 35-38; column 2, lines 21-22). Goldberg further teaches that the morphogenic protein is produced by the expression of a recombinant DNA molecule in a host cell (column 3, lines 50-55). Furthermore, as evidenced by Amano et al. the morphogenic protein, scatter factor (a.k.a. hepatocyte growth factor), is osteogenic.

Although Goldberg et al. does not specifically teach that the morphogenic protein stimulatory factor has a "synergistic and or additive effect" on angiogenesis by the morphogenic protein, it would be expected that such an effect occurs since Goldberg et al. teaches that combinations of the morphogenic protein and FGF provide greater stimulation of endothelial tube formation in vitro than did the same agents used individually (column 8, lines 7-11).

Although Goldberg et al. does not specifically teach that the morphogenic protein is a monomeric species, the claimed peptide appears to be the same as the prior art , absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2-5, 7, 12-15, and 17, 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldberg et al. (US Patent 6,013,624; October 1993, IDS) as evidenced by Amano et al. (Arch Oral Biol., Vol. 44, No. 11, November 1999, abstract only).

1. Goldberg et al. teach as set forth above.
2. Goldberg et al. do not specifically teach the simultaneous administration of the morphogenic protein and the morphogenic protein stimulatory factor to a target locus wherein the target locus is a vascular tissue defect (Claims 17 and 19).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the morphogenic protein (scatter factor) and the morphogenic protein stimulatory factor (FGF) "simultaneously" to a target locus because Goldberg et al. teach that angiogenesis can be enhanced by administering scatter factor in combination with a growth factor (column 3, line 35). One would have been motivated to do so since the combined administration of both compounds at the same time would be

expected to enhance the treatment of a vascular defect such as would healing, organ transplantation, or skin grafting (column 3, lines 40-48).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
June 2, 2001

SUSAN UNGAR, PH.D
PRIMARY EXAMINER